REMARKS

Claims 30-49 are pending in the application. Claims 30, 32-35, 39, 41-43, 47, and 49 have been amended to better describe the invention and for consistency reasons. Favorable reconsideration in light of the amendments and the remarks which follow is respectfully requested.

The Amendments

The independent claims have been amended to better describe the nature of the invention as having multiple constituents composed of more than one chemical species derived from the outer layer of blood or mesothelial cells. The term "the outer layer" refers to the glycocalyx of said cells as explained in the description and cells have only one glycocalyx so that there is one or "the" outer layer.

The Enablement Rejection

Claims 30-49 have been rejected under 35 U.S.C. § 112, first paragraph, for enablement reasons with regard to native heparan sulfate and the transitional phrase. Referring to the arguments presented by the Applicants in the RCE Submission in June 2005, the Examiner asserts that the trace impurities of the native heparan sulfate are not disclosed or claimed. Applicants respectfully disagree to the extent that the impurities have been disclosed. The claims have been amended to more clearly reflect the nature of the invention.

Initially, it is noted that the RCE Submission of June 2005 states "[t]he native heparan sulfate materials contains trace impurities that come from other constituents of the outer layer of a red blood cell and/or mesothelial cell." In this sense, the claims have been amended to reflect that the invention makes use of more than one constituent derived from a mesothelial and/or blood cell. Thus, the subject "impurities" are indeed expressly covered by the amended claim language, which requires "constituents of the outer layer of a blood cell, constituents of the outer layer of a mesothelial cell." The change of singular to plural, i.e. the change from "constituent" to

"constituents" should be allowable since the claims as originally filed clearly contain the wording "constituents". The claims as originally filed are attached. However for a reason we cannot follow the plural term was changed to singular without any necessity to do this.

The term "isolation" (Examples 1-4) is a term of art in the biological sciences. As stated in the RCE Submission of June 2005, this invention is distinguished by the use of "native heparan sulfate materials." Native biomolecules are functional and have biological activity; such native biomolecules are functional due to specific and general affinity for binding to other species in the biological milieu that is due to their native tertiary structure. The traditional chromatography and precipitation techniques described in Examples 1-4 are universally understood to only ENRICH the targeted group of biomolecules relative to the other elements in the biological milieu. It is a common term of art in the biological sciences to refer to a sample that has been enriched with a particular component to a high degree (for example, at least 80%) as having "isolated" that particular constituent. It is recognized as a virtual impossibility to purify from endogenous tissue proteins, glycoproteins, DNA, RNA, etc. to 100% purity without using harsher techniques that destroy their native structure. Even recombinant proteins expressed with high binding affinity tags cannot be purified from expression hosts to 100% purity and DNA precipitation never yields DNA that is completely free of contaminating proteins and histones.

Moreover, Examples 1 and 3 expressly describe in a manner sufficient to teach one skilled in the art how to isolate such constituents. That is, the methods of preparing the mixture of glycocalyx "constituents", i.e. the mixture of the constituents of the outer layer of blood or mesothelial cells of the claims as described in the specification contains the subject impurity materials. As described by the specification, the preparation of constituents of the outer layer of a blood cell and/or constituents of the outer layer of a mesothelial cell result in a final fraction that contains MULTIPLE constituents, some of which can include the subject "impurities". Whatever impurities are present in the materials are derived from the disclosed mesothelial and/or blood

cells and are consistently present as the inevitable byproduct of the preferred embodiments in the specification. No experimentation needs to be done to prepare the materials required for the invention. One reasonably skilled in the art knows that impurities are present in any *in situ* preparation.

Concerning the term "impurities" it has to be stressed that the mixture of constituents of the outer layer of mesothelial cells or blood cells does not contain "impurities" per se. A basic idea of the invention relates to transfering the glycocalyx of a mesothelial cell or a blood cell, i.e., to transfer the complete constituents (= all constituents) of the outer layer (= glycocalyx) of a mesothelial cell or of a blood cell, which have to be hemocompatible to an artificial or natural surface in order to make this surface hemocompatible. Consequently, all constituents of the outer layer (glycocalyx) of a mesothelial cell or of a blood cell are used since all these constituents have to be hemocompatible. The invention is uses easily obtainable mesothelial cells or blood cells which are enzymatically shaved (i.e. the constituents of the outer layer of these cells are cleaved enzymatically) and thereafter the intact cells but without glycocalyx are separated from the glycocalyx constituents and after removing the enzyme solution the mixture of all glycocalyx constituents are used as coating material for surfaces of, for instance, medical implants such as stents in order to make these surfaces blood-compatible (=hemocompatible). Therefore, the claimed mixture of constituents of the outer layer of a mesothelial cell or of a blood cell does not contain "impurities"; instead, the mixture contains all single constituents of the outer layer while it could be that some of these constituents are not exactly characterized. However there may be some constituents which are not fully chemically characterized, but these constituents are part of the undoubtfully hemocompatible native outer layer and thus of the invention and should not necessarily be regarded as "impurities".

Once again, a basic aspect of the invention is to isolate all constituents of the outer layer (glycocalyx) of a mesothelial cell or of a blood cell and to transfer this hemocompatible outer layer to a surface of an artificial or natural material in order to make the surface hemocompatible. Within this process all constituents (chemically

characterized or not) are used as coating material and not only a single constituent which may comprise "impurities" in form of other minor constituents of the outer layer of a mesothelial cell or blood cell.

Finally, as noted by MPEP § 2111.03, the transitional phrase "consisting of" excludes any element, step, or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931). MPEP § 2111.03 further notes *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) that clearly explains that "consisting of" functions to close the claim to the inclusion of materials other than those recited except for impurities ordinarily associated therewith.

The "constituents" of the claims are adequately described in the specification in a manner so that one skilled in the art can MAKE and USE the constituents, so long as the constituents come from the outer layer of a blood cell or the outer layer of a mesothelial cell. It is not a requirement of the patent laws to know the chemical identity of every species in the invention so long as the preferred embodiment allows one to practice the invention and obtain the utility thereof.

The Adequate Description Rejection

Claims 30-49 have been rejected under 35 U.S.C. § 112, first paragraph, for not adequately describing the transitional phrase and heparan sulfate.

With regard to the transitional phrase, the Examiner asserts that the term "consists of" is not described in the specification. Applicants respectfully disagree. While the words "consists of" may not be present in the specification, this fact does NOT mean that the transitional phrase "consists of" cannot be used. The phrase "consists of" is a legal term that has inherent support in the word "containing" (numerous instances including page 3, line 32 in the specification). In other words, changing the transitional phrase from "comprising" to "consisting essentially of" or to "consists of" is a legal maneuver, and it is NOT necessary to have the words "consisting essentially of" or "consists of" in the specification to make such an amendment.

Furthermore, the general description of the hemocompatible surface in the specification provides support for the amended claim of a hemocompatible surface consisting of at least one of an artificial compound, a natural organic compound, or an inorganic compound and constituents of the outer layer of a blood cell, constituents of the outer layer of a mesothelial cell or a combination thereof. It should be noted that the specification (see, for example, page 6, lines 22-24) recites to "constituents" and originally filed claim 1 also recited "constituents." Therefore, the specification as originally filed provides adequate support for the claims in their present form, and indicates that the inventors had possession of the invention at the time of filing.

The First Art Rejection

Claims 30-36, 38, 39, 41-47, and 49 have been rejected under 35 U.S.C. § 102(b) or § 103(a) over Baumann et al. Baumann et al relates to endothelial cell surface heparan sulfate (ESHS) bonded to oligoamide spacers which are in turn anchored to a synthetic polymer surface. The oligoamide spacer of Baumann et al has a 16-atom chain length for the cellulose surface and an 11-atom chain length for the silicon surface.

To establish anticipation, each and every claim feature must be disclosed in a single cited art document. The independent claims require a hemocompatible surface consisting of two elements: namely, 1) at least one of an artificial compound, a natural organic compound, or an inorganic compound and 2) a constituent of the outer layer of a blood cell, a constituent of the outer layer of a mesothelial cell or a combination thereof. Generally speaking, the first element is the surface while the second element renders the surface hemocompatible.

Baumann et al fails to disclose, teach, or suggest hemocompatible surfaces with only the two required elements. In particular, Baumann et al requires the presence of oligoamide spacers. The function of the "consisting of" transitional phrase is to EXCLUDE the use of oligoamide spacers in hemocompatible surfaces. Since Baumann et al does not disclose all of the claimed features, Baumann et al cannot

anticipate any of the claims. A full copy of the Baumann et al article is enclosed to facilitate the Examiner's consideration of this rejection.

The Examiner argues that the Baumann et al oligoamide spacer bonded to a surface, e.g. silicon, is equivalent to the surface of the first element (an artificial compound) while the ESHS is equivalent to the second element which renders the surface hemocompatible. Baumann et al is a scientific paper and the limits of what are disclosed is not set forth in standard claim language. Nevertheless, reading Baumann et al to indicate that the surface co-valently modified with oligoamide spacer is equivalent to the unmodified surface of the first element of the current invention (artificial compound) is a tortured construction of what is disclosed in Baumann et al.

The process disclosed in Baumann et al explicitly requires three parts in transforming the material to hemocompatibility: a surface commonly used in the art, modification of that surface with oligoamide spacer, and only then rendering the surface hemocompatible by bonding of ESHS. Stated simply, the extra expense and effort required to make a surface co-valently modified with oligoamide spacer excludes the possibility of Baumann et al containing the same claim element as the inexpensive and readily available surface of the first element of the invention. Baumann et al fails to disclose the first element of the invention. The second element of the invention requires constituents derived from the outer layer of a blood and/or mesothelial cell. Baumann et al discloses the use of ESHS constituent derived from an ENDOTHELIAL and not a blood or mesothelial cell. Since Baumann et al does not disclose all of the claimed features, Baumann et al cannot anticipate any of the claims.

With regard to obviousness, the independent claims further stipulate the positioning of the constituents relative to at least one of an artificial compound, a natural organic compound, or an inorganic compound. Specifically, the claims require that the constituents are firmly attached to the artificial compound, the natural organic compound, or the inorganic compound by at least one of chemical immobilization, photoimmobilization, adhesion, and drying. Baumann et al fails to teach or suggest that its ESHS is firmly attached to its synthetic polymer surface. Instead, Baumann et al

teaches that its ESHS is attached to oligoamide spacers, and it is the oligoamide spacers which are attached to its synthetic polymer surface. This is important because attaching ESHS to a synthetic polymer surface, and then attaching ESH to the oligoamide spacers would NOT have suggested to one skilled in the art to firmly attach a constituent to the surface of an artificial compound, natural organic compound, or inorganic compound directly.

Furthermore, there are many disadvantages associated with using ESHS compared to using the hemocompatible constituents of the claimed invention. The preparation of ESHS requires the cultivation of endothelial cells and therefore ESHS can only be obtained in small quantities. Additionally, successful purification of ESHS is difficult to achieve. This is because the purification process is very time consuming, laborious, and cost intensive. Consequently, the combination of these factors makes ESHS coatings too expensive for commercially viable mass production. It is noted that solid phase synthesis or recombinant synthesis of ESHS is also not commercially useful as it is also too complicated and too expensive.

Furthermore the Baumann et al coating process is not commercially applicable, since ESHS can only be obtained in small quantities which are not sufficient to coat medical implants. Therefore endothelial cells have to be cultivated which is a time consuming process and also cost intensive. The endothelial cells have to be collected and the ESHS has to be isolated. The artificial or natural surface has to be modified to bear functional groups to which the linker and than the ESHS can be bound. This complex procedure may work in a laboratory but is not useful at all for commercial purposes. In this regards, the Baumann et al publication is a scientific paper of a university Professor doing basic research and explaining his complex theories, but is not a paper of a company describing the method for obtaining new hemocompatible medical devices. Until now, no company was interested in the complex technology disclosed by Baumann et al. This is because of the fact, that the Baumann et al publication is not commercially applicable and no person skilled in the art would take a procedure which is not commercially applicable into consideration for coating medical

devices. Since intellectual property rights protect new, inventive and commercially applicable inventions, the commercial applicability is one important aspect of inventions and an inventor would not use methods which are clearly not commercially applicable. Therefore a skilled artisan would refrain to take the complex Baumann et al method into consideration.

For these reasons, there are currently no products coated with ESHS available in the hemocompatible surfaces market. Therefore, ESHS is, at this time, merely an academic project and has made no significant contribution to technological progress in the field of hemocompatible surfaces.

Given the significant disadvantages of ESHS, those of skill in the art would not use ESHS as a hemocompatible coating and instead would choose to use the commercially viable synthetic heparin, since cultivation of endothelial cells and isolation of ESHS and purification of ESHS takes too much time, is too expensive, and results in too low yield which makes the ESHS not suitable for commercial use as coating material.

In addition, the independent claims state that the hemocompatible material be derived from "constituents of the outer layer of a blood cell, constituents of the outer layer of a mesothelial cell or a combination thereof." Baumann et al only discloses material obtained from aortic endothelial cells and not from blood or mesothelial cells. Therefore, Baumann et al would NOT have suggested to one skilled in the art to look towards more easily obtained blood cells and mesothelial cells as a source for hemocompatible material.

Further Baumann et al teaches the use of a pure fraction of endothelial cell surface heparan sulfate (ESHS). As explained above the claimed invention is directed to the use of multiple constituents of the outer layer of a blood cell or the outer layer of a mesothelial cell to form a hemocompatible surface. Thus the use of only the single ESHS fraction as disclosed in Baumann et al does not anticipate the claimed invention. Nowhere does Baumann et al even suggest the use of multiple constituents of the outer cell layer. In fact Baumann et al expressly **teaches against** the use of multiple

constituents. Baumann clearly states that the unfractionated heparin (HE) showed high platelet adhesion and thrombus formation *in vitro* whereas the purified ESHS fraction showed no platelet adhesion. Therefore, one skilled in the art would have been taught from Baumann et al to avoid the use of multiple constituents to form a hemocompatible coating as claimed in the invention.

Thus the use of only the single ESHS fraction as disclosed in Baumann et al does not make obvious the claimed invention of a hemocompatible coating consisting of multiple constituents of a blood cell or mesothelial outer layer.

In contrast to Baumann et al, the claimed invention provides a significant step forward in technological progress in the field of hemocompatible surfaces. The claimed invention provides a fully hemocompatible surface that is not only simple to produce, but is also produced from source materials that are cheap and available in large quantities.

In light of the differences between the claims and Baumann et al, one skilled in the art would not have been motivated by Baumann et al to make the novel hemocompatible surfaces of the claims. And since Baumann et al does not teach or suggest hemocompatible surfaces consisting of two elements: namely, 1) at least one of an artificial compound, a natural organic compound, or an inorganic compound not hereto subjected to any special chemical treatment and 2) constituents of the outer layer of a blood cell, constituents of the outer layer of a mesothelial cell or a combination thereof, and since Baumann et al does not teach or suggest the relative positioning of these two elements, Baumann et al cannot render the claims obvious.

Moreover, unexpected advantageous effects of the claimed glycocalyx constituents (constituents of the outer layer of mesothelial cells or blood cells) over the ESHS of Baumann et al can be shown. A test for thrombogenicity was used wherein an artificial surface was coated either with ESHS or with our glycocalyx constituents. The ESHS coated surface showed a reduction of platelet aggregation on the surface of about 50% in comparison with an uncoated surface. Surprisingly, the surface coated with the inventive constituents of the outer layer of mesothelial cells or blood cells

showed a reduction in platelet aggregation of about 80% in comparison to the uncoated surface. The platelet aggregation is linear correlated with the thrombogenicity.

A possible explanation for this unexpected result could be that platelet aggregation is initiated by different proteins in the blood which adsorb to the non-hemocompatible surface. These proteins comprise, for instance, albumin, immunoglobulines, fibronectin, fibronogen, high molecular weight fibrinogen. In the case that the non-hemocompatible surface is coated with ESHS, the aggregation of some but not all of the proteins is prevented, which initiate platelet aggregation. However, if the non-hemocompatible surface is coated with all constituents of the glycocalyx, the adhesion of all proteins can be prevented and consequently the platelet aggregation is lower in comparison to the surface coated with ESHS.

The Second Art Rejection

Claims 37, 40, and 48 have been rejected under 35 U.S.C. § 103(a) over Thompson in view of Baumann et al. Thompson relates to making a prosthesis that is made of metal, polymeric monofilaments or polymeric multifilament yarns. Thompson fails to teach or suggest hemocompatible surfaces consisting of two elements: namely, 1) at least one of an artificial compound, a natural organic compound, or an inorganic compound and 2) constituents of the outer layer of a blood cell, constituents of the outer layer of a mesothelial cell or a combination thereof. Thompson also fails to teach or suggest the relative positioning of these two elements.

Claims 37, 40, and 48 are patentable because Thompson does not cure the deficiencies of Baumann et al with regard to the independent claims. Consequently, claims 37, 40, and 48 are patentable for the same reasons that claims 30, 39, and 47 are patentable.

Petition for Extension of Time

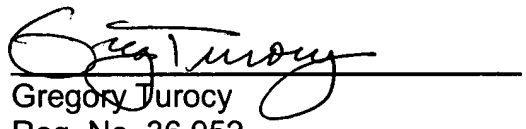
A request for a three month extension of time is hereby made (small entity status has been established). A Credit Card charge form is enclosed herewith to pay the petition fees.

Should the Examiner believe that a telephone interview would be helpful to expedite favorable prosecution, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

In the event any fees are due in connection with the filing of this document, the Commissioner is authorized to charge those fees to our Deposit Account No. 50-1063.

Respectfully submitted,

AMIN & TUROCY, LLP



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